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Systematic Review

Therapeutic and Pharmacological Role of Natural Products in Neurological Diseases: Targeting Autophagy Pathways

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Abstract: The mounting interest in botanical-derived natural products for neuroprotection gains significant attention for their prevalence, diverse array of bioactive constituents, and roles in traditional and modern medicine. While numerous address neuroprotective mechanisms of botanical products, few focus specifically on their autophagy effects. This review conducted a systematic analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies were extracted from the Google Scholar, Scopus, and PubMed databases up to February 28, 2024. Inclusion criteria targeted original English studies examining neuroprotective effects of botanicals associated with autophagy pathways in human clinical studies, *in vitro* models, and *in vivo* models. A total of 104 studies were included, comprising 32 cell-based studies, 52 animal-based studies, and 20 studies that employed both *in vitro* and *in vivo* models. These studies were categorized by botanical families and species, focusing on their neuroprotective activities and specific neurological diseases, including Alzheimer's disease, Parkinson's disease, and stroke. Results show that families such as Fabaceae and Apiaceae were frequently investigated for their autophagy-modulating neuroprotective potential. Notable botanical species, including *Panax ginseng*, *Glycyrrhiza uralensis*, *Polygala tenuifolia*, *Angelica sinensis*, and *Paeonia lactiflora*, have demonstrated promising neuroprotective effects by regulating autophagy processes, including initiation, elongation, maturation, and selective degradation, across neurological disease models. The

review emphasizes the necessity for further investigation into the specific mechanisms by which these botanicals modulate autophagy and their therapeutic applications in neurological diseases. This comprehensive analysis establishes a foundation for future studies developing effective botanical-based interventions targeting autophagy pathways in neurodegenerative diseases.

Keywords: Neuroprotection, Autophagy, Botanical species, Herbs, Plant extracts, Traditional medicine, Alzheimer's disease, Parkinson's disease; SDG 3 Good health and well-being

1. Introduction

Neurological diseases encompass a group of disorders characterized by the progressive degeneration of neurons, ultimately leading to the impairment of their associated functions. These diseases have emerged as a significant global health concern, affecting approximately 1 billion individuals worldwide and contributing to approximately 7.1% of the total global burden of disease[1]. Despite recent advances in modern medicine, effective treatments for neurological diseases remain limited and are often associated with multiple adverse effects. Hence, the lack of current effective neuroprotective strategies has stimulated increasing interest in alternative therapeutic approaches. Among these, the application of botanical crude extracts for neuroprotection has gained significant attention due to their wide diversity, rich bioactive constituents, long-standing history in traditional medicine, and potential applications in modern pharmacology[2].

Natural remedies have long been a common practice in traditional medicine systems worldwide, offering a vast repository of bioactive compounds that demonstrate therapeutic effects. Recent studies have highlighted the neuroprotective properties of various plant extracts, illustrating their ability to enhance neuronal survival and functionality[3]. The increasing focus on these remedies within scientific research is particularly evident in the field of neurological diseases, where the pharmacological effects of plant extracts are being extensively investigated for their neuroprotective activities in modulating cellular mechanisms and the pathological conditions associated with disease progression[2].

One of the most intriguing areas of research is the impact of botanical extracts on autophagy pathways, which play a vital role in maintaining cellular homeostasis by degrading and recycling damaged cellular components. Furthermore, dysregulation of autophagy is often implicated in the pathogenesis of various neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis[4]. Targeting autophagy pathways with botanical extracts presents a novel therapeutic strategy for

neuroprotection, as these extracts and their compounds have been shown to modulate autophagic activity and mitigate neurodegeneration[3].

Autophagy has emerged as a significant area of research due to its crucial role in neurodegenerative diseases. There is a growing interest in exploring botanical species that exhibit autophagic neuroprotective activity by targeting pathological mechanisms such as the clearance of toxic protein aggregates, the maintenance of cellular homeostasis, the alleviation of neuroinflammation, and the reduction of neuronal death. Despite the extensive research available, there are limited systematic reviews that gather and compile all these neuroprotective botanical species that modulate autophagic pathways. This systematic review primarily aims to explore, document, and identify the therapeutic and pharmacological roles of botanical extracts in neurological diseases, with a specific focus on their modulatory effects on autophagy pathways. Furthermore, this review seeks to categorize botanicals by family, disease, and mechanism, while highlighting various modulatory autophagic proteins involved. This structured synthesis is intended to guide future therapeutic development.

2. Materials and Methods

2.1. Search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. In simple terms, PRISMA provides a set of evidence-based standards for reporting systematic reviews and meta-analyses of studies focused on healthcare interventions. The research articles of interest were extracted from the Google Scholar, Scopus and PubMed databases, covering the period from the inception of these databases until February 28, 2024. The protocol used for the electronic search is illustrated in Figure 1. Information regarding the search terms and filters is presented in Supplementary Information Table S1 and S2. PRISMA checklist is presented in Supplementary Information Table S3:

2.2. Study Selection

The study selection process was assessed by two reviewers independently. The studies meeting the following criteria were considered potentially eligible for this systematic review:

2.2.1. Inclusion criteria:

a. Original studies in article format.
b. Articles at the final publication stage.
c. Studies reported in English language only.

d. Application of botanical species in neuroprotective studies with autophagy linkage.
e. Neuroprotective studies based on human clinical studies, *in vitro* cell model and *in vivo* animal model.
f. No restrictions were placed on the year of publication of the studies.

2.2.2. Exclusion criteria:

a. Reviews, virtual screening, letters, case studies, conference papers, opinions, reports, or editorial papers.
b. Studies that used non-botanical species.
c. Studies that used pure compounds instead of botanical crude extracts.
d. Studies that examined other benefits of botanical species unrelated to neuroprotection.
e. Neuroprotective studies that did not examine the autophagy pathways.

2.3. Data Extraction

Full-text screening was performed by two reviewers to extract data from the included studies. The data input for the systematic review encompassed the common and scientific taxonomy of the botanical species, the parts of the species used, their origin, types of extracts, and their preparation methods, as well as studies on phytochemical constituents. The study settings, specific experimental models employed, examined autophagy mechanisms, and other neuroprotective activities of the botanical species were included. Additionally, all reported plant names were cross-checked to ensure the accuracy of species identification and plant taxonomy using The World Flora Online (https://www.worldfloraonline.org/).

3. Results

3.1. Search Results

Figure 1 shows the search strategy flow and its result. The search resulted in a total of 2850 studies which were available from inception to 2024. During the screening process, a total of 2688 studies were excluded based on title and abstract review, and 162 studies were further excluded after full-text screening. Hence, a total of 104 studies were included in this systematic review that consist of 32 cell based studies, 52 animal based studies, and 20 both *in vitro* and *in vivo* studies. Supplementary Information Table S4 presents the autophagy-modulating protective activities of all recorded botanicals. It also includes information such as plant taxonomy, sample preparation methods, identified bioactive compounds, mode of study, type of diseases studied. In the subsequent article analyses, botanical species reported to have neuroprotective activity with autophagy were categorized based on their family and species levels (Table 1). Additionally, the types of neurological diseases investigated using these botanical species were analyzed (Table 2).

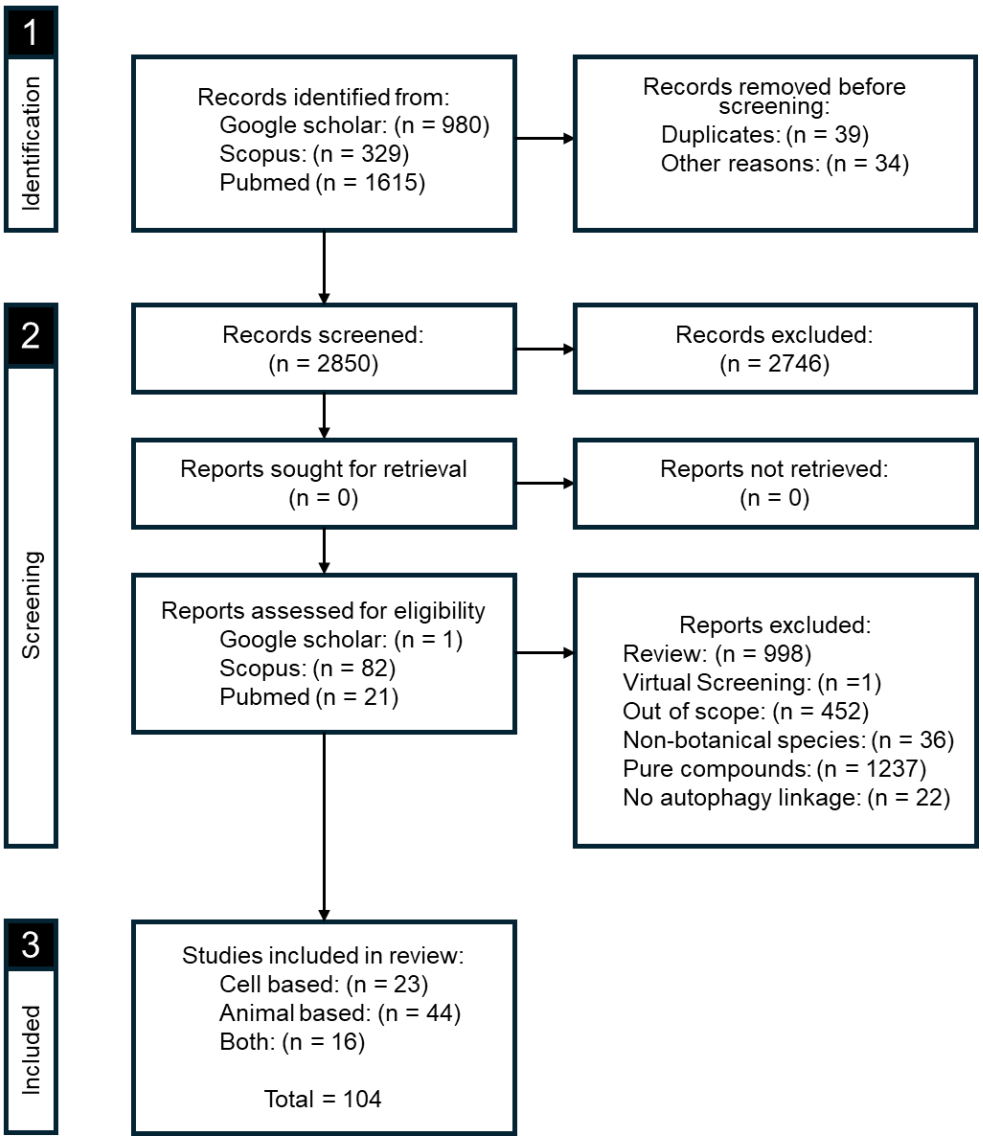

Figure 1. PRISMA flow chart.

Table 1. Representatives of recorded plant families by number of species and the recorded studied plant species that reported potential neuroprotective potentials.

Family	Number of species	Species*	Number of publications
Apiaceae	9	*Panax ginseng*	11
Fabaceae	9	*Angelica sinensis*	7
Rutaceae	6	*Glycyrrhiza uralensis*	7
Asteraceae	5	*Polygala tenuifolia*	7
Ranunculaceae	4	*Atractylodis macrocephala*	6
Brassicaceae	3	*Paeonia lactiflora*	6
Solanaceae	3	*Bupleurum chinese*	5
Zingiberaceae	3	*Ginkgo biloba*	5

Family	Number of species	Species*	Number of publications
Acoraceae	2	*Lycium babarum*	5
Apocynaceae	2	*Scutellaria baicalensis*	5
Campanulaceae	2	*Coptis chinensis*	4
Crassulaceae	2	*Dendrobium nobile*	4
Ericaceae	2	*Gardenia jasminoides*	4
Polygalaceae	2	*Acorus gramineus*	3
Polygonaceae	2	*Angelica dahurica*	3
Rubiaceae	2	*Astragalus membranaceus*	3
Acanthaceae	1	*Astragalus propinquus*	3
Alpinia	1	*Carthamus tinctorius*	3
Amaranthaceae	1	*Cistanche deserticola*	3
Aristolochiaceae	1	*Glycyrrhiza glabra*	3
Berberidaceae	1	*Zingiber officinale*	3
Lauraceae	1	*Aconitum carmichaelii*	2
Magnoliaceae	1	*Acorus calamus var. angustatus Besser.*	2
Malvaceae	1	*Angelica tenuissima*	2
Menispermaceae	1	*Asarum heterotropoides Fr. Var. mandshuricum*	2
Myrtaceae	1	*Cimicifuga heracleifolia*	2
Orchidaceae	1	*Cinnamomum cassia*	2
Orobanchaceae	1	*Dimocarpus longan*	2
		Euterpe precatoria	2
		Ligusticum wallichii	2
		Magnolia officinalis	2
		Phellodendron chinensis	2
		Pinellia ternate	2
		Pinus succinifera	2
		Portulaca oleracea	2
		Prunus cerasus	2
		Pueraria lobata	2
		Salviae miltiorrhizae	2
		Tlaspi arvense	2
		Withania somnifera	2

One each for the following: *Alpinia oxyphylla, Angelica gigas, Anemarrhena asphodeloides, Apocynum venetum, Coffea arabica, Arctium lappa, Vaccinium sect. Cyanococcus, Boswellia serrata, Bacopa monnieri, Bambusa textilis, Calendula officinalis, Callerya nitida, Camellia sinensis, Celosia argentea, Chaenomeles sinensis, Citrus aurantium, Citrus bergamia, Citrus unshiu, Clausena lansium, Clitoria ternatea, Codonopsis pilosula, Conioselinum anthriscoides, Crataegus pinnatifida, Curcuma aromatica, Curcuma longa, Cynanchum otophyllum, Ephedra sinica, Epimedium brevicornu, Eucommia ulmoides, Euphorbia pekinensis, Forsythia suspensa, Fragaria ananassa, Graptopetalum paraguayense, Herba Rhodiolae, Hibiscus mutabilis, Homalomena occulta, Hordeum vulgare, Humulus lupulus, Isatis indigotica, Juglans regia, Ligusticum chuanxiong, Litchi chinensis, Lonicera japonica,*

Mentha haplocalyx, Neolitsea cassia, Nicandra physaloides, Olea europaea, Ophiopogon japonicus, Oxalis corniculata, Paeonia suffruticosa, Paeonia veitchii, Panax notoginseng, Paullinia cupana, Phragmites communis, Phoenix dactylifera, Piper longum, Piper nigrum, Platycodon grandiflorus, Polygonum cuspidatum, Polygonum multiflorum, Prunus amygdalus, Prunus persica, Psoralea corylifolia, Punica granatum, Raphanus sativus, Rehmannia glutinosa, Rheum officinale, Salvia sahendica, Saposhnikovia divaricata, Schisandra chinensis, Scrophularia buergeriana, Selaginella tamariscina, Sideritis scardica, Stephania tetrandra, Tanacetum cinerariifolium, Ugni molinae, Urtica dioica, Vaccinium corymbosum, Verbena officinalis, and Ziziphus jujuba.

Table 2. Types of neurological diseases investigated.

Neurological diseases	Number of publications
Alzheimer's disease	21
Parkinson's disease	15
Stroke	14
Neuropathology	8
Depression	8
Neurotoxicity	8
Amyotrophic lateral sclerosis	7
Huntington’s disease	4
Neuroblastoma	4
Dietary-related brain injury	3
Aging	2
Spinal cord injury	2
Allergic rhinitis	1
Autism	1
Dementia	1
Diabetic peripheral neuropathy	1
Epilepsy	1
Hypoxia	1
Lumbar disc herniation	1
Retinal disorders	1

4. Discussion

4.1. Comparative Analysis of Autophagic Pathways Activation

Modulation of autophagy pathways by various botanical species is a complex process that involves distinct stages, each characterized by specific genes and proteins critical to the initiation, nucleation, elongation, maturation, and selective degradation of autophagy. In this review, we present a series of modulations by the documented botanical extracts that influence different stages of autophagy. Figure 2 compiles autophagy modulators regulated by botanical extracts in both gene expression and protein expression levels.

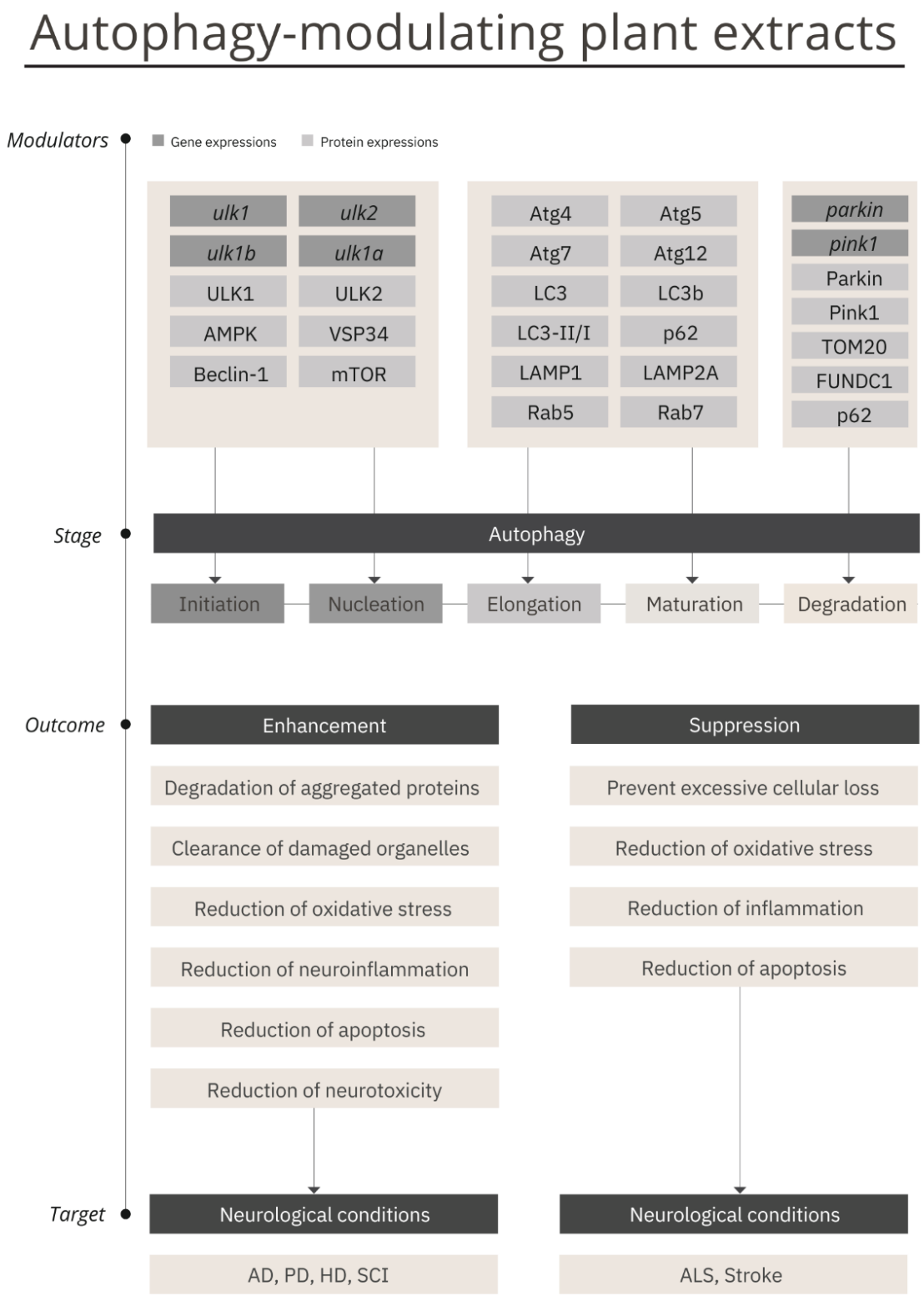

Figure 2. Neuroprotective activities of recorded botanicals in modulating autophagy mechanisms in various neurological diseases.

4.1.1. Modulation of autophagy stage: initiation and nucleation

The first stage of autophagy, known as initiation, is characterized by the formation of phagophores. They are the membrane structures that engulf damaged cytoplasmic components, including organelles and proteins[5]. The subsequent stage, nucleation, involves the formation of double-membrane phagophores taking place[6,7]. Several key modulatory proteins, such as ULK1, ULK2 and AMBRA1a, play a crucial role in initiating this process. These initiator proteins primarily activate the formation of the ATG13-FIP200 complex, which integrates upstream signals to initiate the autophagy pathway[8,9]. For example, *Calendula officinalis* L. and *Eucommia ulmoides* Oliver have been revealed to activate the expressions of the genes *ulk1*, *ulk1b*, *ulk2*, and *ambra1a*, thereby promoting autophagy[10,11]. In contrast, *Litchi chinensis* Sonn. and Pien Tze-Huang, a traditional Chinese medicine, have been demonstrated to enhance the expression of the ULK1 protein[12,13]. Additionally, VPS34 and Beclin-1 (BECN1) are essential modulatory proteins involved in the formation of pre-autophagosomal formation and the initiation of autophagy[14,15]. Our review indicates that Beclin-1 is one of the most frequently studied modulatory markers. Numerous studies have shown that various botanical species increase both the gene and protein expression of Beclin-1, significantly enhancing autophagy activity[10,16–48]. Conversely, VPS34 has been less extensively investigated according to our review, despite its crucial role as a lipid kinase in initiating the autophagy process. For example, *Acorus tatarinowii*, *Folium Hibisci* mutabilis, and *Lonicera japonica* have been found to enhance VPS34 expression, thereby promoting autophagy[34,49,50].

The AMPK (AMP-activated protein kinase) and mTOR (mechanistic target of rapamycin) signaling pathways are widely studied in relation to autophagy, as highlighted in our review. AMPK serves as a key regulator of cellular energy homeostasis and is activated under low-energy conditions, such as during nutrient deprivation or metabolic stress, which are closely associated with the hallmarks of cellular pathogenesis in neurological diseases[51]. Under these conditions, AMPK is activated through phosphorylation, which subsequently inactivates the mTOR pathway. When the mTOR pathway is inactivated, there is a further reduction in ULK1 expression, leading to the initiation of autophagy[52]. Our review indicates that numerous studies have demonstrated the ability of various botanical species to activate the AMPK pathway[13,19,22,36,53–55]. This activation subsequently inhibits the mTOR pathway, thereby promoting autophagic enhancement effects[12,13,22,26,44,53,56–63].

4.1.2. Modulation of autophagy stage: elongation and maturation

The elongation phase is the stage during which the phagophore expands and engulfs cytoplasmic materials, while the maturation stage results in the formation of a double-membrane

structure known as the autophagosome. This process is primarily facilitated by a series of autophagy-related proteins (Atg proteins) and LC3 (light chain 3) proteins. Both types of proteins share similar functions that trigger membrane expansion and cargo recruitment[64,65]. Our review demonstrated that numerous botanical species have the ability to enhance the upregulation of Atg protein expressions, including Atg4, Atg5, Atg7, and Atg12[11,18,23,34,45,46,63,66–70].

On the other hand, the conversion of LC3-I to LC3-II is a signature hallmark of autophagy elongation. The cytosolic form of LC3-I merges with phosphatidylethanolamine (PE) to form LC3-II, which is then incorporated into the autophagosomal membrane[71]. Hence, LC3 expression has become the most widely utilized autophagy marker in clinical studies. Based on our review, the majority of studies investigate the LC3-II/I ratio, as it provides a precise indication of autophagy activation status. The botanical species with autophagy-enhancing properties that can increase the expression of LC3, LC3B, and the LC3-II/I ratio are listed[12,13,16,18,19,21–27,29,31,33–35,37–42,45–47,50,53,55,58,59,61,63,66,67,70,72–88]. Furthermore, the presence of LC3-II provides binding sites for various autophagy receptors, such as p62 (also known as sequestosome 1, SQSTM1). Once docking is complete, the p62 protein facilitates the selective engulfment of ubiquitinated cargo for the subsequent maturation process[71]. Consistent studies have demonstrated that the activation of LC3 proteins results in a reduction in p62 expression. This occurs because p62 itself functions as a substrate for autophagic degradation; thus, increased autophagy activity necessitates the loss of p62 protein.

In the maturation stage, the process involves the fusion of mature autophagosomes with lysosomes or endosomes to form autolysosomes, where the degradation of engulfed materials occurs[65]. During this process, two crucial lysosomal-associated membrane proteins (LAMPs), namely LAMP1 and LAMP2A, participate to complete the fusion process, thereby enhancing autophagic flux[89]. Based on our review, *Cynanchum otophyllum* Schneid, *Coffea arabica* Burundi, *Humulus lupulus* L., and *Vaccinium sect. Cyanococcus* was observed to induce autophagic flux by increasing the expression of LAMP family proteins[37,47,80,85]. Another key protein, Rab7, assists in the fusion of autophagosomes and lysosomes, representing the ultimate step in the maturation process[90,91]. Despite the lack of in-depth studies on the Rab family, it stands out as a potential specific biomarker for identifying the maturation stage of autophagy. For instance, *Apios americana* Medik induced autophagic flux by increasing the expression of Rab5 proteins.

4.1.3. Modulation of selective autophagy: mitophagy and aggrephagy

Selective autophagy is defined as a specialized form of autophagy that specifically degrades certain types of cellular component. For example, mitophagy targets and degrades

mitochondria, while similar principles apply to ER-phagy, ribosomal autophagy, and aggregophagy. This process allows cells to maintain homeostasis and respond effectively to specific stressors. In this section, we will focus exclusively on mitophagy and aggregophagy, as their markers were identified in our review.

Mitophagy is the selective degradation process of mitochondria through autophagy, which is essential for maintaining mitochondrial integrity. This process ensures the removal of damaged or dysfunctional mitochondria, thereby preventing the production of excessive ROS that can contribute to cellular stress and the subsequent activation of apoptosis[92,93]. Key regulators such as PTEN-induced putative kinase 1 (PINK1) and the Parkin protein. PINK1 accumulates on the outer mitochondrial membrane, where it recruits Parkin, which then ubiquitinates mitochondrial proteins. The ubiquitinated mitochondria are subsequently recognized for autophagic degradation[92]. Our review demonstrated that botanical species known to enhance autophagy induced the expression of both PINK1 and Parkin genes and proteins, thereby activating mitophagy[10,11,59,67,84,88]. Furthermore, the studies we reviewed also examined the protein expression levels of TOM20 and FUNDC1 which serve as specific receptors for mitophagy. Our findings indicated that the botanical species *Thunbergia laurifolia* and *Scrophularia buergeriana* Miquel can increase the expression of TOM20 and FUNDC1 receptors, respectively[84,94].

Aggregophagy is a form of selective autophagy that specifically degrades aggregated or misfolded proteins, thereby reducing their accumulation in cells and contributing to various neurodegenerative diseases[93,95]. Furthermore, the upregulation of p62 expression has been demonstrated to enhance the regulation of aggregated proteins, including Aβ, α-synuclein, and Huntingtin. In the following section, we highlight the botanical species that have been studied for their potential to decrease p62 expression and enhance autophagy[67,96].

4.1.4. Transcriptional regulation of autophagy

Transcriptional regulation of autophagy is a critical process that governs the modulation of autophagy-related gene (ATG) expression by various transcription factors and signaling pathways. The transcription factors and signaling pathways discussed in our review include FoxO1, FoxO3A, and TFEB. Forkhead box (FOX) proteins are among the major transcription factors that enhance autophagy; they are activated in response to oxidative stress and nutrient deprivation. The FOX proteins primarily stimulate the expression of several ATGs, thereby promoting autophagy and enhancing cellular resistance to various stresses. Based on our review, botanical species such as *Apios americana* Medik and *Dendrobium nobile* Lindl elicit a similar autophagic enhancement effect *via* upregulation of FOXO1 expression[42,69]. Additionally, the downregulation of FOXO3 expression by Danhong Chinese medicine has been observed to lead

to an autophagic suppression effect[97]. TFEB is another principal regulator that functions to enhance lysosomal biogenesis and autophagy by activating of multiple autophagic-enhancing genes[98–100]. For instance, *Cynanchum otophyllum* Schneid has been shown to enhance autophagy through the upregulation of TFEB expression[85].

Collectively, the modulation of autophagy pathways by various botanical species demonstrates their versatility in targeting different stages of autophagy, including initiation, nucleation, elongation, maturation, and selective degradation. This review emphasizes the key roles of the studied proteins and transcription factors, such as Beclin-1, LC3, and p62, in regulating these processes. Furthermore, it provides a comprehensive overview and insights into the use of appropriate markers for detecting and differentiating various stages of autophagy. Our review also highlights that the actions of these autophagic-modulating botanical species do not target a single autophagic marker but rather influence multiple markers throughout the entire process. This suggests that the autophagic regulators and associated pathways are interrelated and essential for completing the autophagy cycle. Consequently, it underscores the need for in-depth studies on the effects of botanical extracts on autophagy by targeting multiple autophagic markers that represent different stages, in order to understand the specific modes of action of various autophagic-modulating botanical extracts.

On the other hand, our review mainly compiles and reveals various autophagic-modulating botanical extracts that may help rebalance cellular homeostasis and mitigate neuropathological pathways. We have highlighted their potential therapeutic activities in different neurological diseases models that could be attenuated through autophagic modulation. In terms of botanical families, we found that the Fabaceae and Apiaceae are the most extensively studied in neuroprotective research. Several interrelated factors may explain the research on these two botanical families, including their significant species diversity, their role in human diets, and their widespread use in traditional medicine[101,102]. The Fabaceae family encompasses a diverse array of species, many of which are commonly used as cooking ingredients. Notable examples of Fabaceae plants include beans, lentils, and peas. The importance of legumes as a dietary component has prompted to extensive research into this family, as they not only provide protein but also contain a wealth of bioactive compounds, such as flavonoids, isoflavones, and phenolic acids, which offer significant benefits to the human body. Similarly, the Apiaceae family is renowned for its culinary herbs and spices, including parsley, coriander, and cumin. This family includes approximately 3000 recorded and cultivated species worldwide[103,104]. Generally, Apiaceae plants contain essential oils and flavonoids that demonstrate promising pharmacological properties, including antioxidant and anti-inflammatory effects, which further support their role in neuroprotection[105].

Furthermore, our findings indicate that *Panax ginseng*, *Glycyrrhiza uralensis*, *Polygala tenuifolia*, *Angelica sinensis*, *Paeonia lactiflora*, and *Atractylodis macrocephala* are the top six species being reviewed in our study. Interestingly, these studies are originated from China, likely due to the extensive use of herbs in traditional Chinese medicine (TCM), where they have been recognized for their beneficial effects on mental health since the ancient times. For example, *Panax ginseng* is well-known Chinese herb that has been documented to enhance cognitive functions and reduce fatigue, while *Glycyrrhiza uralensis* is valued for its calming effects in attenuating stress responses[106]. Similarly, *Polygala tenuifolia* is traditionally used for mental clarity and has been scientifically proven to improve memory and alleviate anxiety[107]. *Angelica sinensis* also known as "female ginseng," demonstrates blood-nourishing benefits and is believe to support emotional well-being[108]. *Paeonia lactiflora* is well known for its anti-inflammatory properties and has traditionally been utilized in the treatments related to mood and cognition[109]. Lastly, *Atractylodis macrocephala* is conventionally utilized to maintain overall mental health by improving digestive function and enhancing vitality. Furthermore, the combination of these species in TCM formulations identified in our review, including Bu Shen Jie Du Fang, Bu Shen Huo Xue, Chaihu-Longgu-Muli, Kai Xin San, modified Xiaoyao San, Wen Shen Jian Pi, and Xiao Xu Ming, exhibits significant neuroprotective effects, particularly in stroke models, and enhances human mental health through autophagy modulation[18,58,110–114].

4.2. Neuroprotective Potentials Across Neurological Diseases

4.2.1. Neuroprotective potentials across neurological diseases: autophagy enhancement

In the context of autophagy dysregulation, this process can be either excessively activated or inhibited, significantly impacting neuronal health. An imbalance in autophagy is invariably associated with a range of neurological disorders, underscoring the critical importance of maintaining optimal autophagic function. The review demonstrated that botanical extracts have the potential to rebalance autophagy mechanisms, thereby promoting neuronal health. In studies utilizing models of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, the accumulation of toxic protein aggregates is a hallmark pathological feature. The enhancement of autophagy through the effects of botanical extracts in these contexts facilitates the degradation of these aggregates, clears damaged organelles, and reduces oxidative stress, thereby alleviating disease progression. Furthermore, in conditions characterized by neurotoxicity, oxidative stress, and spinal cord injury, the application of botanical extracts in both in vitro and in vivo models have been shown to enhance autophagy and promote cell survival by removing damaged cellular components and supporting cellular repair.

It is noteworthy that in certain models of depression, the enhancement of autophagy by botanical extracts has been linked to mood regulation through the removal of dysfunctional mitochondria and the support of neurogenesis. In the context of neurological cancers, including brain tumors and neuroblastoma, the modulation of autophagy plays a pivotal role in influencing tumor progression and treatment responses. Enhanced autophagy induced by botanical species is frequently observed in anti-cancer models, as it facilitates the degradation of damaged organelles and proteins, thereby promoting cell survival under stress conditions. Additionally, these extracts contribute to their anti-proliferative effects through the generation of reactive oxygen species (ROS) and the induction of endoplasmic reticulum stress pathways. Figure 2 shows the general neuroprotective activities of recorded botanical extracts in enhancing and supressing autophagy pathways to alleviate different neurological diseases.

4.2.1.1. Alzheimer's disease

Our review indicates that Alzheimer's disease is the most prevalent research topic concerning the neuroprotective effects of botanical extracts. This disease is characterized by the accumulation of misfolded amyloid-beta (Aβ) and hyperphosphorylated Tau proteins, which result in the overproduction of ROS, the activation of neuroinflammation, and ultimately, neuronal cell death[115,116]. *In vitro* experiments have demonstrated botanical species that enhance autophagy increase the viability of various cell models subjected to Aβ treatment[13,19,25,37,47,53,55,80]. Among the botanical species studied, *Litchi chinensis* Sonn. has been demonstrated to decrease the neuroinflammatory response *via* NLRP3 downregulation in multiple cell lines and mouse brain tissues under Aβ treatment[13,19]. On the other hand, *Pinus succinifera* has exhibited to exhibit anti-apoptotic and antioxidant properties, as evidenced by a reduction in the Bax/Bcl-2 expression ratio and caspase activation, along with an increase in antioxidant enzyme activity[25]. *In vivo* behavioral studies have demonstrated that the neuroprotective effects of autophagy-enhancing botanical species can reduce Aβ-induced paralysis in the *C. elegans* model[49,117], while also improving spatial learning, cognitive function, and memory in rodent models of AD[5,13,14,21,34,46,84,96]. Notably, *Cynanchum otophyllum* Schneid, *Dendrobium nobile* Lindl, *Ginkgo biloba* 761, *Graptopetalum paraguayense*, *Oxalis corniculate*, *Scrophularia buergeriana*, and Yi Zhi Fang Dai Chinese medicine have been shown to enhance the clearance of Aβ and Tau plague in the brain tissues[5,14,21,55,84,85,96].

4.2.1.2. Parkinson's disease

Parkinson's disease is typified by the selective loss of dopaminergic neurons in the substantia nigra. Its pathophysiology is complex and involves not only the loss of dopaminergic neurons but also the accumulation of misfolded proteins known as alpha-synuclein[118,119]. It is

the second most abundant studied disease based on our review, we found that most of the botanical species displayed neuroprotective effects *via* prevent cell loss due to α-synuclein deposition *in vitro*[16,18,40,87,120]. From the list above, *Nicandra physaloides* and *Pinus succinifera, Piper Longum* L. demonstrated anti-apoptotic activity *via* reducing apoptotic cells, caspase activation and Bax/Bcl-2 ratio expression[40,120,121]. The antioxidant and mitochondrial surveillance activities were also reported in *Pinus succinifera* and *Piper Longum* L. respectively [40,121]. Significantly, *Polygala tenuifolia* increased the clearance of mutant α-synuclein deposition in PC-12 cell model[67]. In animal model studies, significant improvement the behavioral function and brain dopaminergic markers were shown after treatment of botanical extracts in PD rodent models[36]. Importantly, botanical species such as *Boswellia serrata* improved the clearance of aggregated α-synuclein in PD rodents' brain tissues, highlighting their potential autophagic mode of action in targeting PD pathogenesis.

4.2.1.3. Huntington's disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms. The etiology of Huntington's disease is primarily attributed to the production of a mutant form of the huntingtin protein, which contains an abnormally long polyglutamine (polyQ) tract[122]. According to this review, *Polygala tenuifolia* and *Ugni molinae* exhibited neuroprotective activities in HD cell models *via* decreasing the aggregation of the mutant polyQ tract and huntingtin protein within the cells[67,123]. In animal studies, *Paullina cupana* displayed neuroprotective effects by enhancing the viability of neurons responding to aversive stimuli in the *C. elegans* model of HD[117]. Our review indicates that there is limited research focusing on botanical species in the context of Huntington's disease, which may be overshadowed by more prevalent neurological diseases such AD and PD. Nevertheless, HD warrants increased attention in the field of neurodegenerative research due to its shared pathogenesis with AD and PD. Given that certain botanical species have shown a significant role in the clearance of aggregated proteins, they could serve as promising therapeutic agents for HD.

4.2.1.4. Spinal cord injury

Spinal cord injury (SCI) represents a significant health concern, resulting from trauma to the spinal cord. This injury can lead to a range of debilitating consequences, including loss of motor and sensory functions, autonomic dysregulation, and a diminished quality of life. The pathological processes that follow an SCI are complex and involve a cascade of cellular events, including inflammation, oxidative stress, and neuronal apoptosis. These processes contribute to secondary injury mechanisms that exacerbate tissue damage and functional impairment[124,125].

Enhanced autophagy has been associated with neuroprotection and recovery following injury, as it facilitates the clearance of damaged cells and promotes tissue repair. For instance, our review indicated that the autophagic-enhancing properties of Crataegus pinnatifida significantly improved the condition of SCI rats by reducing neuronal injury and inducing axonal regeneration of injured spinal motor neurons, thereby enhancing SCI rats' motoneuron function in these rats. Additionally, it exhibited anti-apoptotic activity by preventing the formation of apoptotic cells[39].

4.2.1.5. Oxidative stress

Oxidative stress is defined as a condition characterized by an imbalance between the production of reactive oxygen species (ROS) and the ability to detoxify these reactive intermediates or repair the resulting damage. In the context of various neurological diseases, oxidative stress is well-documented as a key factor in the initiation and progression of pathological processes[126]. Autophagy is activated in response to oxidative stress as a protective mechanism to eliminate damaged components and reduce cellular toxicity[127,128]. For instance, elevated levels of ROS can trigger inflammatory responses, disrupt mitochondrial function, and promote the aggregation of misfolded proteins, all of which are hallmarks of neurodegeneration [129]. Botanical species that possessed a wide range of natural antioxidants have emerged as potential therapeutic agents in combating oxidative stress and enhancing autophagy. In this review, *Apios americana* Medik, *Apocynum venetum, Psoralea coryfolia* L., and *Salvia sahendica* have shown promising antioxidant activity in reducing intracellular ROS production in various cell models while increasing cell viability from oxidative damage[43,66,69,78]. Collectively, these botanical extracts displayed similar protective properties in combating oxidative stress, primarily by enhancing anti-apoptotic effects through the inhibition of mitochondrial-mediated apoptosis pathways.

4.2.1.6. Neurotoxicity

Neurotoxicity is defined as the exposure to various harmful substances that pose a significant risk to neuronal health and contribute to the pathogenicity of neurodegenerative diseases. Substances such as aluminum, glutamate, d-galactose, and benzo[a]pyrene have been demonstrated to induce oxidative stress, inflammation, and neuronal apoptosis. While neurotoxicity is not a disease in itself, it is a condition plays a role in to the pathogenesis of various neurodegenerative diseases[126,130,131]. Based on our review, various botanical species have been demonstrated to enhance autophagic activity, providing a protective effect against neurotoxic agents. Aluminum is a common neurotoxin; exposure to aluminum can lead to cognitive decline and neurodegeneration. Previous studies have indicated that aluminum can disrupt calcium homeostasis and promote oxidative damage[132]. In a preclinical study, *Andrographis paniculata*

was shown to protect the viability of PC12 cells and improve cognitive and memory function in ICR mice subjected to aluminum chloride insult. Significantly, histopathological assays showed that ROS level and p-Tau protein accumulation were reduced following treatment with *Andrographis paniculata* extract[86]. Glutamate, while essential for normal neurotransmission, can lead to excitotoxicity when present in excess, resulting in neuronal injury and death[133]. Two previous studies have revealed that both *Selaginella tamariscina* and *Thunbergia laurifolia* extracts elicit neuroprotective effects against glutamate-induced neurotoxicity in HT22 cells. For instance, these autophagy-enhancing species reduced intracellular ROS level, improved mitochondrial function and decreased the activation of apoptosis[94,134].

D-galactose is frequently employed in experimental models to simulate the processes of aging and oxidative stress, which together result in significant damage to the nervous system[135]. On the other hand, manganese chloride has been extensively documented as a neurotoxic agent. A substantial body of evidence indicates that exposure to manganese chloride leads to the generation of reactive oxygen species (ROS), which subsequently cause damage to neurons[136]. In our review, we found that the *Dendrobium nobile* Lindl consistently activated autophagy and elicited neuroprotective activities against both D-galactose and manganese chloride-treated cell models. For examples, *Dendrobium nobile* Lindl extract decreased senescence biomarkers and increased cell viability in D-galactose-treated primary hippocampal neurons, while reducing intracellular ROS level and apoptotic activation, thereby improving cell viability in manganese chloride-treated PC-12 cells[42,67]. Benzo[a]pyrene, a polycyclic aromatic hydrocarbon and neurotoxic compound, induces the production of ROS reactive to trigger neuronal injury[137]. In our review, *Bacopa monnieri* has demonstrated its neuroprotective effects by reducing apoptotic cells in benzo[a]pyrene-treated primary human fetal astrocytes and increasing the lifespan of benzo[a]pyrene-treated *C. elegans*[77].

Collectively, botanical species that demonstrated neuroprotective effects against neurotoxicity show significant potential for addressing neurodegenerative diseases. This is due to the fact that these botanical extracts not only enhance autophagic activity but have also been shown to display broader range of neuroprotective activities, including antioxidant effects, anti-inflammatory properties, and the enhancement of mitochondrial function.

4.2.1.7. Neurological cancer

Neurological cancers typically exhibit a more aggressive nature and complex pathophysiology compared to other types of cancers, posing significant challenges to the research field. One of the most common types of neurological cancer is brain tumors, which can arise from various cell types within the central nervous system. This diversity results in multiple clinical

manifestations based on their location, size, and histological characteristics[138,139]. On the other hand, neuroblastoma is also a type of neurological cancer characterized by malignant tumors that primarily affects children. This cancer originates from neural crest cells within the sympathetic nervous system. According to our review, various botanical species have displayed anti-proliferative effects against brain tumors and neuroblastoma cell models *via* activation of autophagy and apoptosis. For examples, *Gardenia jasminoides* exerted anti-proliferative activity on glioblastoma cell lines without compromising the viability of normal astrocyte cells; it also increased the activation of caspases and pro-apoptotic proteins[75]. Similarly, *Sideritis scardica* demonstrated anti-proliferative effects on glioma cell line while preserving the viability of primary rat astrocytes, primarily through the activation of apoptosis and an increase in ROS level in the glioma cells[76]. On the other hand, *Angelica polymorpha* Maxim, *Clausena lansium* (Lour.), *Posidonia oceanica* (L.) Delile, *Tanacetum cinerariefolium* show anti-proliferative properties on human SH-SY5Y neuroblastoma cells by targeting mitochondrial-mediated apoptosis. This includes increased ROS levels, reduced mitochondrial function, and the activation of caspases and pro-apoptotic proteins[22,23,79,140]

4.2.2. Neuroprotective potentials across neurological diseases: autophagy suppression

Conversely, excessive autophagy can be detrimental in diseases such as amyotrophic lateral sclerosis (ALS), stroke, and epilepsy, as it may lead to neurodegeneration and cell death. Our review shows that botanical extracts can suppress autophagy, potentially protecting neurons from excessive damage. Additionally, our review indicates that most botanical species exhibit autophagy suppression in stroke models, which can be attributed to the specific pathological contexts of ischemic and hemorrhagic strokes. The excessive autophagy activated by stroke can lead to further neuronal loss and contribute to the progression of neurodegenerative diseases. Hence, interventions aimed at suppressing the autophagy pathway represent the most effective strategy for addressing conditions of excessive autophagy.

4.2.2.1. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the degeneration of both upper and lower motor neurons. This condition can cause numerous clinical symptoms such as muscle weakness, atrophy and ultimately, respiratory failure. Unfortunately, this disease is typically fatal, with the majority of patients unable to survive more than five years after the initial onset of symptoms[141]. One of the most distinctive pathological hallmarks of ALS is the accumulation of misfolded proteins, specifically superoxide dismutase 1 (SOD1) and TDP-43. Similar to other aggregated proteins, these misfolded proteins can disrupt normal cellular function, induce oxidative stress, and ultimately lead to neuronal cell

death[142]. According to our review, various botanical species promote autophagy suppression, which modulates the pathophysiological processes associated with ALS. For examples, *Chaenomeles sinesis Olea europaea* L, Korean herbal medicine, and the Wen-Shen-Jian-Pi Chinese medicinal formula have been shown to improve motoneuron function, decrease inflammatory proteins, increase muscle fibres, extend lifespan in ALS mouse models[57,114,143,144]. Interestingly, some botanical species that promote autophagy enhancement have also been reported to improve ALS condition. For instances, *Withania somnifera* increased the lifespan of ALS mice and the viability of their motor neurons, while also enhancing the clearance of misfolded SOD1 proteins in ALS mouse models[72]. The *Bojungikgi-tang* Korean herbal medicine consistently displayed neuroprotective activities in two ALS studies by reducing neuroinflammatory marker and decreasing apoptotic activation, thereby suppressing muscle denervation and motoneuronal loss in ALS mouse models[56,60].

4.2.2.2. Stroke

Stroke, which includes both ischaemic and haemorrhagic types, is a leading cause of morbidity and mortality worldwide. Ischemic stroke is characterized by a reduction in cerebral blood flow, resulting in a lack of oxygen and nutrients to the brain, which leads to neuronal damage. In contrast, hemorrhagic stroke occurs due to the rupture of blood vessels, causing bleeding in or around the brain. Both forms of stroke can result in significant neurological deficits. The pathophysiological processes involved include oxidative stress, inflammation, and neuronal apoptosis[145,146]. Generally, we found that botanical extracts exhibiting neuroprotective activities in stroke models suppressed the autophagy pathway, decreased inflammation, and reduced cell apoptosis, thereby improving the neurological function and alleviating stroke-related pathological changes in *in vivo* models. For instance, *Ginkgo biloba* EGB1212, *Lycium barbarum*, Danhong Chinese medicine, Tong Shen Tablets, Pien Zhe Huang Chinese medicine, Shengmai injection, Xiao Xu Ming, and Yi Qi Huo Xue Chinese medicine have shown these effects[97,110,147]. In contrast, some botanical species demonstrated similar neuroprotective effects in stroke models by inducing the autophagy pathway, such as *Arctium lappa* L., *Ginkgo biloba* 761, *Angelica sinensis* (Oliv.) Diels, and *Cinnamomum cassia* (L.) J. Presl, and Buyang Huanwu Chinese medicine[24,28,33,41,148]. Furthermore, we found that traditional Chinese medicine (TCM) has been prominently utilized in stroke studies, likely due to the high prevalence of stroke cases in China. Additionally, the integration of botanical species within TCM reflects a long-standing practice of using natural remedies to manage stroke and its associated symptoms in the Chinese population, highlighting the potential of botanical species and TCM as effective neuroprotective agents for stroke.

4.3. Summary of Findings

The neuroprotective effects of botanical species in managing various neurological diseases are significant, as they demonstrate protective activities related to neuropathophysiological pathways. For instance, these species exhibit the ability to combat ROS, maintain mitochondrial function, reduce inflammation, and decrease apoptosis. Additionally, the modulatory effects of botanical extracts on autophagy have a substantial impact on improving cognitive function and alleviating neuronal damage. This highlights the potential of botanical species as novel therapeutic or preventative agents in addressing neurological diseases and enhancing patient outcomes. However, further research is necessary to fully elucidate their mechanisms of action and optimize their use in clinical settings, as specific neuroprotective actions have yet not been clearly defined.

Moreover, there is no fixed formula for how botanical species exert their neuroprotective effects in the context of autophagy modulation. Instead, the dysregulated autophagy observed in various neurological conditions can be either activated or suppressed by botanical species, depending on the specific circumstances and severity of the condition. For instance, the activation of autophagy by certain botanical species, which helps maintain neuronal health, often involves the degradation of misfolded proteins and damaged organelles. Conversely, some botanical extracts may exert neuroprotective effects by suppressing autophagy, particularly in conditions where excessive autophagy could lead to cell death. Furthermore, our review has shown that different types of botanical species may either upregulate or suppress autophagy while still achieving similar neuroprotective outcomes, as evidenced by studies on ALS and stroke. This variability suggests that the mechanisms of action of these botanical species may target pathways upstream of autophagy, thereby providing an appropriate response in autophagy modulation[149]. However, further research is needed to identify the specific signaling pathways involved and to determine how diverse botanical extracts or compounds can be optimized for therapeutic use in neurodegenerative diseases and acute neurological injuries.

4.4. Therapeutic Implications and Future Directions

The potential therapeutic applications of botanical species in clinical settings, particularly in the field of neuroprotective research, are increasingly being recognized. Among the botanical species analyzed in our review, *Ginkgo biloba* and *Withania somnifera* (ashwagandha) have consistently demonstrated significant neuroprotective effects across multiple experimental models. For instance, *Ginkgo biloba* extracts have been reported to enhance cognitive function, reduce neuroinflammation, and promote autophagy for the clearance of misfolded protein clearance, making it a potential treatment for Alzheimer's disease[27,46]. Additionally, it has been

shown to improve neurological function, prevent neuronal injury, and enhance recover in post-stroke conditions[41,150]. Similarly, *Withania somnifera* has demonstrated the ability to enhance motor neuron viability and decrease oxidative stress in Parkinson's models, while also mitigating neuroinflammation and promoting clearance of SOD1 misfolded proteins in ALS models[32,72].

Various challenges must be acknowledged throughout the process of therapeutic development utilizing botanical species (Table 3). Firstly, the transition of botanical extracts or compounds from preclinical to clinical trials often presents significant challenges due to their low efficacy in human subjects. While animal models can provide valuable insights into the mechanisms of action and potential efficacy of neuroprotective agents, they frequently fail to accurately replicate the complexities of actual human neurological diseases. Secondly, optimizing extraction and formulation techniques to enhance bioavailability is a crucial consideration, and investigating synergistic combinations of diverse botanical extracts, such as TCM formulations could help to maximize therapeutic outcomes[151]. Furthermore, the specific molecular mechanisms through which these botanicals' species exert their effects remain a significant gap in knowledge, despite their wide range of neuroprotective activities demonstrated in preclinical trials. Therefore, by deepening our understanding of these botanical species and their interactions with biological systems, we can provide insights to address these research gaps and challenges effectively.

For future directions, the primary focus will be on conducting comparative studies of pure compounds derived from potential botanical species, particularly in the context of identifying neuroprotective agents (Table 4). Although phytochemical analyses of these botanical species have been reported in the included studies, the information remains superficial when the neuroprotective effects of the bioactive compounds are not investigated. Therefore, identifying the active neuroprotective compounds enhances our understanding of how these botanicals exert their beneficial effects on neuronal health and function. Actionable processes begin with phytochemical isolation and validation to identify the structure and neuroprotective activity of pure compounds from botanical extracts. Secondly, structural studies, such as structure-activity relationship (SAR), can analyze the structural features that correlate with the neuroprotective activity of pure compounds[152]. Utilization of metabolomics and network pharmacology can facilitate the identification of the active compounds responsible for the observed effects and improve our comprehension of their mechanisms of action[153]. Subsequent research into the neuroprotective properties of botanical species should focus on transitioning the active compounds to clinical trials. Through systematic clinical trials, the safety, bioavailability, and effectiveness of the tested compounds in human populations can be thoroughly elucidated[154].

Moreover, our review found that pharmacokinetic studies on botanical extracts or compounds are insufficient. However, the research is crucial, particularly in the context of neuroprotective studies, due to the inherent challenges posed by the blood-brain barrier (BBB). The BBB serves as a selective barrier that regulates the entry of substances into the central nervous system. Furthermore, numerous compounds that demonstrate promising effects *in vitro* may not effectively penetrate this barrier *in vivo*, thereby limiting their therapeutic potential[155]. Therefore, it is essential to identify neuroprotective bioactive compounds that can reach the brain, indicating their ability to permeate BBB and exert therapeutic effects. Research strategies involve the use of *in vitro* BBB models, including monolayer, coculture, and even three-dimensional (3D) cell models of various brain endothelial cells, to preliminary assess the permeability of compounds across the BBB[156,157]. This is followed by the assessment of BBB permeability using *in vivo* models, employing intravenous injection methods and brain perfusion techniques[158]. Advanced imaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission-computed tomography (SPECT), enable the visualization of the distribution of radioactive-labeled compounds in animal models[159].

Additionally, understanding the pharmacokinetics of bioactive compounds is vital for determining their bioavailability, distribution, metabolism, and excretion. These factors ultimately influence the brain bioavailability and efficacy of compounds within the central nervous system. Conversely, molecular docking studies are highly recommended for future research, especially in neuroprotective investigations aimed at overcoming the challenges posed by BBB. This computational technique enables researchers to predict the specific biological targets of bioactive compounds, which can inform their neuroprotective mechanisms of action by targeting specific proteins or pathways, thereby providing insights into their potential efficacy and binding affinity[160]. Last but not least, conducting multiple toxicity studies and standardization processes (extraction, isolation, and formulation) to ensure the safety profile of bioactive compounds are essential prerequisites for advancing to clinical trials[161,162]. In the design of these trials, small-scale studies could be conducted to re-evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy in human subjects with specific neurological conditions[163]. Moreover, the incoporation of biomarker studies such as neuroinflammatory markers and neurotrophic factors, serve as valuable are indicators for monitoring treatment responses[164,165].

Table 3. Key challenges in developing therapeutic applications of botanicals.

Aspect	Challenges
Transition from preclinical to clinical trials	• Low efficacy of botanical extracts or compounds in human subjects compared to preclinical models. • Animal models poorly mimic the complexities of human neurological diseases
Optimization of extraction and formulation techniques	• Poor bioavailability of botanical compounds. • Synergistic combinations of botanical extracts (e.g., TCM formulations) require deeper investigation to maximize therapeutic outcomes.
Understanding of molecular neuroprotective mechanisms	• Limited knowledge of specific neuroprotective molecular mechanisms of botanical species • Significant knowledge gap despite well-established neuroprotective activities reported in preclinical trials • Blood brain barrier (BBB) challenges

Table 4. Future directions for advancing therapeutic applications of botanicals.

Future Directions	Research strategies
Pure compounds comparative studies	• Phytochemical isolation (HPLC, LC-MS) and structural validation (NMR, MS) • Structure-activity relationship (SAR) • Mechanistic studies (metabolomics and network pharmacology) • Comparative assessment using *in vitro* and *in vivo* models
Blood-brain barrier related studies	• BBB permeability *in vitro* study using co-culture endothelial, pericytes and astrocytes • BBB permeability animal study using imaging techniques (MRI, PET, SPECT) or biodistribution study • Molecular docking and simulations • Prodrug design to enhance BB permeability of pure compounds
Translation to clinical trials	• Pure compounds processing standardization such as extraction, isolation and formulation • Toxicity studies to establish safety profile of pure compounds • BBB permeability, pharmacokinetics and pharmacodynamic studies, preliminary efficacy and biomarkers assessment (neuroinflammatory markers, neurotrophic factors) in human subjects targeting specific neurological conditions

5. Conclusions

In conclusion, this systematic review presents a comprehensive analysis of the neuroprotective effects of botanical extracts and their combinations, with a primary focus on their autophagic-modulating activities across various neurological diseases. The studies reviewed include both *in vitro* and *in vivo* models for preclinical trials, highlighting their potential to enhance neuronal health and combat neurodegeneration. However, a notable gap was identified in these studies is the absence of clinical trials assessing the efficacy of these extracts in human populations. Furthermore, there is a lack of comparative studies examining the effects of whole extracts versus isolated pure compounds to identify their effective bioactive components. Therefore, future research should prioritize the identification and pharmacokinetic studies of potential neuroprotective agents to understand their absorption, distribution, metabolism, and excretion, particularly to address the challenges posed by the BBB.

Supplementary Materials: Table S1: Search term table for Scopus, PubMed, and Google Scholar. Table S2: Search term filters for Scopus, PubMed, and Google Scholar. Table S3: PRISMA checklist. Table S4: Neuroprotective and autophagy modulatory activities of natural products.

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